

- 57. (New) The method of claim 56, wherein said positive selection microbeads and negative selection microbeads each comprise at least one antibody.
- 58. (New) The method of claim 57, wherein said antibody of said negative selection microbeads binds to the surface of white blood cells.
- 59. (New) The method of claim 58, wherein said antibody of said positive selection microbeads binds to the surface of cells.
- 60. (New) The method of claim 59, wherein said cells are selected from the group consisting of cancer cells, and fetal cells.

Remarks

After canceling the previously pending claims and submitting new claims 39-60, claims 39-60 are now pending this application. Claim 39 is now the sole independent claim that recites, among other things, a method of harvesting target components of a biological sample comprising the use of positive selection microbeads and negative selection microbeads, wherein the positive selection microbeads and the target components become located within a density-specific focusing device for subsequent aspiration. The submission of new claims 39-60 does not constitute new matter in this application, as support for these claims is found throughout the specification and the originally presented claims. For example, support for new claims 39-60 can be found in at least paragraphs 0031, 0037, 0048, 0050, 0055, Figures 1-5 and original claims 1-36. Additionally, the cancellation of the previously pending claims is not to be taken as an acquiescence to the Examiner's previous rejections. Rather, the cancellation of the previously pending claims and the presentation of the new claims is solely to expedite prosecution.

Applicants request consideration and allowance of the newly presented claims in view of the following remarks.

The Examiner's Rejection of Claims 1, 5-13 and 14-18 is Moot

In the Office Action dated October 7, 2003, the Examiner rejected claims 1, 5-13 and 14-18 under 35 U.S.C. §103 as obvious over Levine et al. (USPN 5,635,362) ("Levine 1") in view of Van Vlasselaer (USPN 5,474,687) ("Van Vlasselaer"). Claims 1, 5-13 and 14-18 have been cancelled, thus the rejection is now moot.

In response to the Examiner's rejection of claims 1, 5-13 and 14-18, Applicants reiterate and incorporate by reference the arguments and comments made in response to this rejection presented in their response after final office action, received at the Office on January 29, 2004. Applicants also offer these additional remarks regarding the obviousness rejection. To establish a case of *prima facie* obviousness, the Examiner must meet three criteria. First, the Examiner must show that the references upon which she or he relied teach *every* limitation of the currently claimed invention, *In re Royka* 490 F.2d 981, 985 (C.C.P.A. 1974). Second, the Examiner must show that there is some suggestion or motivation in the references themselves, or within the knowledge of one of ordinary skill in the art, to combine the references to arrive at the claimed invention. Lastly, the Examiner must show that there is a reasonable expectation of success in combining the references, and that this expectation of success is found in the references as well. *In re Vaeck* 947 F.2d 488, 493 (Fed. Cir. 1991). Applicants assert that the Examiner has not met any of these criteria and thus can not sustain an assertion that the claims are obvious to one of ordinary skill in the art.

Specifically, the cited reference of Levine 1 and Van Vlasselaer, alone or in combination, do not teach each and every limitation of the previously pending claims or the currently pending claims. Van Vlasselaer teaches the combination of a special centrifuge tube and a density gradient solution to separate blood into layers. Levine 1 teaches a "density marker" (Levine 1, Col 3, ll. 13-14) to simply identify (but not harvest) cells that are located in various density layers of a centrifuged sample. Neither Levine 1 nor Van Vlasselaer could possibly be combined to produce a method harvesting cells comprising the use of a density-specific channel, passage or bore to *elongate* targeted layers in a sample, as the combination of Levine 1 and Van Vlasselaer does not teach the elongation of layers, among other things. Indeed, the Examiner has seemingly implied that this limitation of elongating layers would distinguish the current invention over

Levine 1 and Van Vlasselaer (*See* Office Action of October 7, 2003, page 6). Contrary to the Examiner's assertions, however, previously pending claims 1, 5-13 and 14-18 had *always* claimed that the passage was for receiving *and elongating* the layers of the sample. Currently pending claims 39-60 maintain this originally presented limitation.

Furthermore, even if every element of the currently claimed invention was taught by the combination of Levine 1 and Van Vlasselaer, these circumstances would not render the invention obvious, since there must be "some teaching, suggestion, or motivation to combine the references." *In re Rouffet*, 149 F.3d 1350, 1355 (Fed. Cir. 1998). *See In re Dow Chem. Co.*, 837 F.2d 469, 473 (Fed. Cir. 1988) (what is needed is a reason, suggestion, or motivation in the prior art that would motivate one of ordinary skill to combine the cited references, and that would also suggest a reasonable likelihood of success in making or using the claimed invention as a result of that combination). Because not all of the elements of the previously or currently claimed invention are found anywhere in Levine 1 or Van Vlasselaer, there can be no motivation in either patent to produce the claimed invention with a reasonable likelihood of success. Indeed, the combination of the Levine 1 and Van Vlasselaer does not even produce the claimed invention. One of ordinary skill would not look to Van Vlasselaer to cure the deficiencies of Levine 1 to arrive at the current invention. Further, even if all the elements of the current invention were found in the combination of Levine 1 and Van Vlasselaer, there is no explicit or inherent motivation, in either of the references or in the art, to combine the references to produce the claimed invention. Thus, the references could not possibly teach or even suggest the claimed invention to one of ordinary skill in the art.

Finally, the Examiner, in making the rejection, glosses over the requirement that there be a reasonable expectation of success in combining the cited references. Indeed, the Examiner simply states that "[o]ne would have a reasonable expectation of success...because both [references] use the similar method to achieve cell separation." (Prosecution History of Serial No. 09/756,590, Office Action of October 7, 2003, page 5). The Examiner's statement, however, is really nothing more than an assertion that Levine 1 and Van Vlasselaer are, at most, analogous art to each other and to the currently claimed invention. Taken to its conclusion, therefore, the Examiner seems to be asserting incorrectly that a reasonable expectation in combining references

will always exist, provided the references are analogous art. Beyond this incorrect assertion, the Examiner has not asserted any other reason that the combination of Levine 1 and Van Vlasselaer would result in the currently claimed invention with any reasonable expectation of success.

In sum, the combination of Levine 1 and Van Vlasselaer does not teach each and every element of the currently or previously claimed invention. There is no motivation to combine Levine 1 and Van Vlasselaer; and the Examiner has not provided any reasoning that one of ordinary skill would be able or motivated to combine Levine 1 and Van Vlasselaer with any reasonable expectation of success. Thus, the Examiner's burden of proof in establishing that the invention of the current application is obvious, in view of Levine 1 and Van Vlasselaer, has never been satisfied.

The Examiner's Rejection of Claims 19-22 and 24-30 is Moot

In the Office Action dated October 7, 2003, the Examiner rejected claims 19-22 and 24-30 under 35 U.S.C. §103 as obvious over Levine et al. (USPN 5,393,674) ("Levine 2") in view of Van Vlasselaer (USPN 5,474,687) ("Van Vlasselaer"). Claims 19-22 and 24-30 have been cancelled, thus the rejection is now moot.

In response to the Examiner's rejection of claims 19-22 and 24-30, Applicants reiterate and incorporate by reference the arguments and comments made in response to this rejection presented in their response after final office action, received at the Office on January 29, 2004. Applicants also offer these additional remarks regarding the obviousness rejection. Applicants assert that the Examiner has not met his burden of establishing that the claimed invention is obvious over the references.

Specifically, Levine 2 teaches a density separation tube containing a float "with a through bore". (See Abstract). Levine 2 does not mention or suggest using particulate carriers or microbeads to adjust the density of the desired and/or undesired components such that the desired components are present in the axial passage and that the undesired components are substantially removed from the axial passage after centrifugation. Van Vlasselaer does not cure this deficiency. Rather, Van Vlasselaer teaches the combination of a special centrifuge tube and a density gradient solution to separate blood into layers. Additionally, Van Vlasselaer teaches the

use of “heavy carrier particles...so that such density-adjusted cells would be pelleted during centrifugation.” (Van Vlasselaer, Col. 10, l. 65 – Col. 11, l. 2). Van Vlasselaer does not teach or even suggest, however, the use of beads that bind target components to keep them in solution during centrifugation. Thus, the combination of Levine 2 and Van Vlasselaer do not contain or even suggest each and every element of the currently or previously claimed invention.

Furthermore, even if every element of the currently claimed invention was taught by the combination of Levine 2 and Van Vlasselaer, these circumstances would not render the invention obvious, since there must be “some teaching, suggestion, or motivation to combine the references.” *In re Rouffet*, 149 F.3d 1350, 1355 (Fed. Cir. 1998). Because not all of the elements of the previously or currently claimed invention are found anywhere in Levine 2 or Van Vlasselaer, there can be no motivation in either patent to produce the claimed invention with a reasonable likelihood of success. Indeed, the combination of the Levine 2 and Van Vlasselaer does not even produce the claimed invention. One of ordinary skill would not look to Van Vlasselaer to cure the deficiencies of Levine 2 to arrive at the current invention. Further, even if all the elements of the current invention were found in the combination of Levine 2 and Van Vlasselaer, there is no explicit or inherent motivation, in either of the references or in the art, to combine the references to produce the claimed invention. Thus, the cited references could not possibly teach or even suggest the claimed invention to one of ordinary skill in the art.

Again, the Examiner, in making the rejection, glosses over the requirement that there be a reasonable expectation of success in combining the cited references. Indeed, the Examiner simply states that “one of ordinary skill in the art would have [*sic*] expectation for [*sic*] success to combine [the references]...because both ...disclose the method of density gradient centrifugation...(e.g. analogous art).” (Prosecution History of Serial No. 09/756,590, Office Action of October 7, 2003, page 10). The Examiner’s statement, however, is admittedly nothing more than an assertion that Levine 2 and Van Vlasselaer are, at most, analogous art to each other and to the currently claimed invention. Taken to its conclusion, therefore, the Examiner seems to be asserting incorrectly that a reasonable expectation in combining references will always exist, provided the references are analogous art. Beyond this incorrect assertion, the Examiner has not

asserted any other reason that the combination of Levine 2 and Van Vlasselaer would result in the currently claimed invention with any reasonable expectation of success.

In sum, the combination of Levine 2 and Van Vlasselaer does not teach each and every element of the currently or previously claimed invention. There is no motivation to combine Levine 2 and Van Vlasselaer; and the Examiner has not provided any reasoning that one of ordinary skill would be able or motivated to combine Levine 2 and Van Vlasselaer with any reasonable expectation of success. Thus, the Examiner's burden of proof in establishing that the invention of the current application is obvious, in view of Levine 2 and Van Vlasselaer, has never been satisfied.

The Examiner's Rejection of Claims 31 and 33-36 is Moot

In the Office Action dated October 7, 2003, the Examiner rejected claims 31 and 33-36 under 35 U.S.C. §103 as obvious over Levine et al. (USPN 5,393,674) ("Levine 2") in view of Van Vlasselaer (USPN 5,474,687) ("Van Vlasselaer"). Claims 31 and 33-36 have been cancelled, thus the rejection is now moot.

In response to the Examiner's rejection of claims 31 and 33-36, Applicants reiterate and incorporate by reference the arguments and comments made in response to this rejection presented in their response after final office action, received at the Office on January 29, 2004. Applicants also offer these additional remarks regarding the obviousness rejection. Applicants assert that the Examiner has not met his burden of establishing that the claimed invention is obvious over the references.

In establishing a *prima facie* case of obviousness, the Examiner is reminded that the differences in the prior art and the *claimed* invention are used to gauge obviousness. Indeed, to establish a *prima facie* case of obviousness, the cited references must teach each and every element of the claimed invention. Specifically, "[a]ll the words in a claim must be considered in judging the patentability of that claim against the prior art." *In re Wilson*, 424 F.2d 1382, 1385 (CCPA 1970). Previously pending claims 31 and 33-36, as well as the present claims require the presence of two set of particulate carriers or microbeads that specifically bind constituents of the sample in the separation container. Neither Levine 2 nor Van Vlasselaer, nor a combination

thereof, teaches the use of two set of specifically-binding beads. Furthermore, neither Levine 2 nor Van Vlasselaer, nor a combination thereof, teaches the use of specifically-binding beads or carriers to lift or place the targeted constituents into an elongated passage. Thus, neither Levine 2 nor Van Vlasselaer, alone or in combination, teach or even suggest all the elements of the claimed invention.

Furthermore, even if every element of the currently claimed invention was taught by the combination of Levine 2 and Van Vlasselaer, these circumstances would not render the invention obvious, since there must be “some teaching, suggestion, or motivation to combine the references.” *In re Rouffet*, 149 F.3d 1350, 1355 (Fed. Cir. 1998). Because not all of the elements of the previously or currently claimed invention are found anywhere in Levine 2 or Van Vlasselaer, there can be no motivation in either patent to produce the claimed invention with a reasonable likelihood of success. Indeed, the combination of the Levine 2 and Van Vlasselaer does not even produce the claimed invention. One of ordinary skill would not look to Van Vlasselaer to cure the deficiencies of Levine 2 to arrive at the current invention. Further, even if all the elements of the current invention were found in the combination of Levine 2 and Van Vlasselaer, there is no explicit or inherent motivation, in either of the references or in the art, to combine the references to produce the claimed invention. Thus, the cited references could not possibly teach or even suggest the claimed invention to one of ordinary skill in the art.

Once again, the Examiner, in making the rejection, glosses over the requirement that there be a reasonable expectation of success in combining the cited references. Indeed, the Examiner simply states that “one of ordinary skill in the art would have [*sic*] expectation for [*sic*] success to combine [the references]...because both ...disclose the method of density gradient centrifugation...(e.g. analogous art).” (Prosecution History of Serial No. 09/756,590, Office Action of October 7, 2003, pages 13-14). The Examiner’s statement, however, is simply an assertion that Levine 2 and Van Vlasselaer are, at most, analogous art to each other and to the currently claimed invention. Taken to its conclusion, therefore, the Examiner seems to be asserting incorrectly that a reasonable expectation in combining references will always exist, provided the references are analogous art. Beyond this incorrect assertion, the Examiner has not

asserted any other reason that the combination of Levine 2 and Van Vlasselaer would result in the currently claimed invention with any reasonable expectation of success.

In sum, the combination of Levine 2 and Van Vlasselaer does not teach each and every element of the currently or previously claimed invention. There is no motivation to combine Levine 2 and Van Vlasselaer; and the Examiner has not provided any reasoning that one of ordinary skill would be able or motivated to combine Levine 2 and Van Vlasselaer with any reasonable expectation of success. Thus, the Examiner's burden of proof in establishing that the invention of the current application is obvious, in view of Levine 2 and Van Vlasselaer, has never been satisfied.

The Examiner's Rejection of Claims 1-18 is Moot

In the Office Action dated October 7, 2003, the Examiner rejected claims 1-18 under 35 U.S.C. §103 as obvious over Levine et al. (USPN 5,393,674) ("Levine 2") in view of Van Vlasselaer (USPN 5,474,687) ("Van Vlasselaer"). It is assumed that the Examiner was intending to reject claims 1-3, 5, 7, 9 and 13-18, since claims 4, 6 and 10-12 had previously been cancelled (*See* Response to Office Action of July 14, 2003, Paper No. 13). Claims 1-3, 5, 7, 9 and 13-18 have been cancelled, thus the rejection is now moot.

In response to the Examiner's rejection of claims 1-3, 5, 7, 9 and 13-18, Applicants reiterate and incorporate by reference the arguments and comments made in response to this rejection presented in their response after final office action, received at the Office on January 29, 2004. Applicants also offer these additional remarks regarding the obviousness rejection. Applicants assert that the Examiner has not met his burden of establishing that the claimed invention is obvious over the references.

Specifically, Levine 2 teaches a density separation tube containing a float "with a through bore". (*See* Abstract). Levine 2 does not mention or suggest using particulate carriers or microbeads to adjust the density of the desired and/or undesired components such that the desired components are present in the axial passage and that the undesired components are substantially removed from the axial passage after centrifugation. Van Vlasselaer does not cure this deficiency. Rather, Van Vlasselaer teaches the combination of a special centrifuge tube and a

density gradient solution to separate blood into layers. Additionally, Van Vlasselaer teaches the use of “heavy carrier particles...so that such density-adjusted cells would be pelleted during centrifugation.” (Van Vlasselaer, Col. 10, l. 65 – Col. 11, l. 2). Van Vlasselaer does not teach or even suggest, however, the use of beads that bind target components to keep them in solution during centrifugation. Thus, the combination of Levine 2 and Van Vlasselaer do not contain or even suggest each and every element of the currently or previously claimed invention.

Furthermore, even if every element of the currently claimed invention was taught by the combination of Levine 2 and Van Vlasselaer, these circumstances would not render the invention obvious, since there must be “some teaching, suggestion, or motivation to combine the references.” *In re Rouffet*, 149 F.3d 1350, 1355 (Fed. Cir. 1998). Because not all of the elements of the previously or currently claimed invention are found anywhere in Levine 2 or Van Vlasselaer, there can be no motivation in either patent to produce the claimed invention with a reasonable likelihood of success. Indeed, the combination of the Levine 2 and Van Vlasselaer does not even produce the claimed invention. One of ordinary skill would not look to Van Vlasselaer to cure the deficiencies of Levine 2 to arrive at the current invention. Further, even if all the elements of the current invention were found in the combination of Levine 2 and Van Vlasselaer, there is no explicit or inherent motivation, in either of the references or in the art, to combine the references to produce the claimed invention. Thus, the cited references could not possibly teach or even suggest the claimed invention to one of ordinary skill in the art.

The Examiner, in making the rejection, does not even address the reasonable expectation of success in combining the cited references. The Examiner offers no proof or reasoning as to why one of ordinary skill in the art would have a reasonable expectation in combining Levine 2 and Van Vlasselaer, because no such expectation actually exists.

In sum, the combination of Levine 2 and Van Vlasselaer does not teach each and every element of the currently or previously claimed invention. There is no motivation to combine Levine 2 and Van Vlasselaer; and the Examiner has not provided any reasoning that one of ordinary skill would be able or motivated to combine Levine 2 and Van Vlasselaer with any reasonable expectation of success. Thus, the Examiner's burden of proof in establishing that the

invention of the current application is obvious, in view of Levine 2 and Van Vlasselaer, has never been satisfied.

The Examiner's rejection of Claims 37 and 38 is Moot

In the Office Action dated October 7, 2003, the Examiner rejected claims 37 and 38 under 35 U.S.C. §103 as obvious over Levine et al. (USPN 5,635,362) ("Levine 1") and Levine et al. (USPN 5,393,674) ("Levine 2"). Claims 37 and 38 have been cancelled, thus the rejection is now moot.

In response to the Examiner's rejection of claims 37 and 38, Applicants reiterate and incorporate by reference the arguments and comments made in response to this rejection presented in their response after final office action, received at the Office on January 29, 2004. Applicants also offer these additional remarks regarding the obviousness rejection. Applicants assert that the Examiner has not met his burden of establishing that the claimed invention is obvious over the references.

Levine 1 teaches a "density marker" (Levine 1, Col 3, ll. 13-14) to simply identify (but not harvest) cells that are located in various density layers of a centrifuged sample. Levine 1 does not use particulate carriers or microbeads to harvest cells from a sample, and Levine 2 does not cure this deficiency. Levine 2 teaches a density separation tube containing a float "with a through bore". (*See* Abstract). Levine 2 does not mention or suggest using particulate carriers or microbeads to adjust the density of the desired and/or undesired components such that the desired components are present in the axial passage and that the undesired components are substantially removed from the axial passage after centrifugation. Thus, the combination of Levine 1 and Levine 2 does not contain each and every element of the claimed invention.

Furthermore, even if every element of the currently claimed invention was taught by the combination of Levine 1 and Levine 2, these circumstances would not render the invention obvious, since there must be "some teaching, suggestion, or motivation to combine the references." *In re Rouffet*, 149 F.3d 1350, 1355 (Fed. Cir. 1998). Because not all of the elements of the previously or currently claimed invention are found anywhere in Levine 1 or Levine 2, there can be no motivation in either patent to produce the claimed invention with a reasonable

likelihood of success. Indeed, the combination of the Levine 1 and Levine 2 does not even produce the claimed invention. One of ordinary skill would not look to Levine 1 to cure the deficiencies of Levine 2, and *vice versa*, to arrive at the current invention. Further, even if all the elements of the current invention were found in the combination of Levine 1 and Levine 2, there is no explicit or inherent motivation, in either of the references or in the art, to combine the references to produce the claimed invention. Thus, the cited references could not possibly teach or even suggest the claimed invention to one of ordinary skill in the art.

The Examiner, in making the rejection, does not even address the reasonable expectation of success in combining the cited references. The Examiner offers no proof or reasoning as to why one of ordinary skill in the art would have a reasonable expectation in combining Levine 1 and Levine 2, because no such expectation actually exists.

In sum, the combination of Levine 1 and Levine 2 does not teach each and every element of the currently or previously claimed invention. There is no motivation to combine Levine 1 and Levine 2; and the Examiner has not provided any reasoning that one of ordinary skill would be able or motivated to combine Levine 1 and Levine 2 with any reasonable expectation of success. Thus, the Examiner's burden of proof in establishing that the invention of the current application is obvious, in view of Levine 1 and Levine 2, has never been satisfied.

Conclusion

Applicants have canceled previously pending claims 1-3, 5, 7-9, 13-22, 24-31 and 33-38 and added new claims 39-60. Cancellation of the previous claims and presentation of new claims 39-60 are solely to expedite prosecution and are not an acquiescence to the Examiner's previous rejections. Accordingly, claims 39-60 are now pending in this application. New claims 39-60 are fully supported by the specification and do not introduce new matter.

In view of the claim cancellation and addition of new claims, all of the Examiner's previous rejections are moot.

If additional extensions of time are necessary to prevent abandonment of this application, then extensions of time are hereby petitioned under 37 C.F.R. §1.136(a), and any fees required, including fees for net addition of claims, are hereby authorized to be charged to account number 50-3120.

Should the Examiner believe that further discussion of any remaining issues would advance the prosecution, he or she is invited to contact the undersigned at the telephone number listed below.

Respectfully submitted,

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